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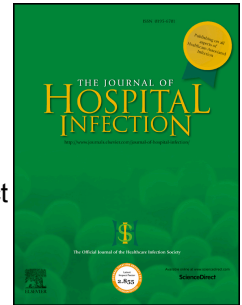
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# Accepted Manuscript

Point of care universal screening for meticillin-resistant *Staphylococcus aureus* (MRSA) on admission wards with a low prevalence of MRSA has no additional impact on MRSA acquisition on those wards compared with culture screening: a cluster randomised cross-over trial

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**Point of care universal screening for meticillin-resistant *Staphylococcus aureus* (MRSA) on admission wards with a low prevalence of MRSA has no additional impact on MRSA acquisition on those wards compared with culture screening: a cluster randomised cross-over trial**

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## SUMMARY

**Background:** Rapid point of care MRSA screening (POCS) at hospital admission may be associated with a reduction in MRSA acquisition rates when compared with slower laboratory-based methods. We conducted a clinical trial to test this proposal.

**Methods:** A cluster randomised cross-over trial in four admission wards of an acute London tertiary care hospital. Polymerase chain reaction based POCS screening was compared with conventional culture screening. Patients were screened on ward admission and discharge and the MRSA acquisition rate on the admission wards was calculated as the primary outcome measure.

**Results:** 10,017 patients were included; 4,978 in the control arm, 5,039 in the POCS arm. The MRSA carriage rate on admission was 1.7%. POCS reduced the median reporting time from 40.4 to 3.7 hours ( $P < 0.001$ ). MRSA was acquired on the admission wards by 23 (0.46%) patients in the control arm and 24 (0.48%) in the intervention arm, acquisition rates of 5.39 and 4.60 per 1000 days respectively. After taking account of predefined confounding factors, the adjusted incidence rate ratio (IRR) for change in trend for MRSA acquisition was 0.961 (95% CI 0.766-1.206). The adjusted IRR for step change for MRSA acquisition was 0.98 (0.304 - 3.162).

**Conclusions:** POCS produces a significantly faster result but has no effect on MRSA acquisition on admission wards compared with culture screening. Where compliance with infection prevention and control is high and MRSA carriage is low, POCS has no additional impact on MRSA acquisition rates over the first 1-4 days of admission compared with conventional culture screening.

## Introduction

Meticillin-resistant *Staphylococcus aureus* (MRSA) infections are associated with greater mortality, morbidity and healthcare costs than similar infections with meticillin-sensitive strains.<sup>1</sup> MRSA is often endemic in healthcare settings and may be transmitted by person-to-person spread. Asymptomatic MRSA carriers are potential, unsuspected sources for transmission and some of them can be identified by admission screening.<sup>1</sup>

In England & Wales, the Health Act (2008) Code of Practice for the prevention and control of health care associated infections requires hospitals to have policies for MRSA admission screening and care pathways for the management of MRSA carriers.<sup>2</sup> The identification, isolation and decontamination of patient carriers are associated with reduced MRSA transmission,<sup>3,4</sup> although the evidence for this is limited and debated.<sup>5-7</sup>

Conventional laboratory-based culture screens (CS) take 2-3 days to report a result. More rapid detection of MRSA carriers theoretically should lead to faster implementation of control procedures and reduce the transmission of MRSA. Screening tests for MRSA using laboratory-based polymerase chain reaction (PCR) have significantly faster turn-around times (TATs) to result, averaging 22 hours.<sup>8</sup> However, although some studies comparing rapid and conventional screening at the same anatomical sites (the majority with nasal screens only) have shown an association between the use of laboratory-based PCR tests and a reduction in MRSA transmission and acquisition rates, others have not.<sup>4,7-12</sup> The lack of effect in some studies may be because of continuing cross-transmission of MRSA during the 22 hour delay before receiving the result of the laboratory-based PCR test. Much of that delay is due to the transit of the specimen between the ward and the laboratory. Because of the conflicting outcome results and the greater expense compared with CS, laboratory-based PCR tests have not been recommended for routine adoption in English hospitals.<sup>13</sup>

Point of care MRSA PCR screening tests (POCS) can be performed on the ward, eliminating specimen transit times and allowing a truly rapid result within about one hour. There have been no reports of controlled studies on this method. We therefore conducted a clinical trial to determine whether performing POCS on hospital wards where a good standard infection prevention and control was in place is associated with a reduction in MRSA acquisition rates compared with CS.

For elective admissions, MRSA screening (and decontamination if necessary) is best done before hospital admission in outpatient clinics where rapid screening is unnecessary. Rapid screening is more appropriate for emergency admissions. In order to achieve better patient management, safety and resource utilisation, many hospitals, including our own, have introduced admission wards. Emergency patients are admitted to these wards for review, investigation and stabilisation before being either transferred to general wards or discharged to outpatient care.<sup>14</sup> Stay on these wards is usually around 24-36 hours. MRSA screening of emergency hospital admissions is therefore ideally done on the admission wards. Since POCS can produce results within one hour, while CS takes 2-3 days, POCS will identify the MRSA status of patients before transfer or discharge and theoretically reduce transmission and acquisition within the general wards. Furthermore, since the postulated advantage of POCS is to reduce the 24-36 hour delay of culture screening, POCS should theoretically reduce MRSA transmission/acquisition on the admission wards themselves.

The impact of admission ward screening on MRSA acquisition on general wards is dependent on numerous uncontrolled factors (including MRSA carriage by elective admissions and general ward transfers) and is difficult or impossible to measure with any accuracy. In contrast, the impact of rapid admission ward screening on MRSA acquisition within the admission wards themselves can be measured fairly accurately by screening at admission and on transfer/discharge and controlling for other variables by using a cross-over trial design. If POCS does have an impact on MRSA transmission compared with CS, then this should occur during the 22-36 hour stay on the admission wards; if it has no effect during this period than

it will have no advantage over culture or laboratory-based PCR screening. We therefore performed a controlled cluster-randomised cross-over clinical trial of POCS compared with CS on the four admission wards in our hospital, with MRSA acquisition on the admission wards as the primary outcome.

## Methods

### *Setting*

The study was performed in a 900 bed, acute NHS London teaching and tertiary care hospital between May 2011 and July 2012. Patients are admitted from the Emergency Department onto one of four admission units. After a period of assessment and treatment on these units, they are either discharged from the hospital or admitted to a general ward. For this study we screened patients on arrival at the admission wards, which were the two Medical Admissions Units (MAUs), the Acute Surgical Unit (ASU) and a Neurosurgical ward, the only study ward with a High Dependency Unit. The characteristics of the wards are shown in Table I.

We used a cluster-randomised, controlled crossover trial design, with the four wards as clusters, randomised to control arm and intervention arm by a computer-generated randomisation list. After the first phase of 7 months, there was a washout period for one month, followed by a second phase of 7 months, in which the wards were crossed over (Figure 1). Assuming a 3% MRSA carriage rate and a 0.3 transmission rate, we estimated that a sample size of 3840 patients per study arm would have an 80% power (at the 5% significance level) to detect a 58% reduction in transmission rate, from 0.3 to 0.126.

In accordance with Ethical Committee approval, all admitted patients were eligible for inclusion after providing informed verbal consent. Staff performing the

screening were trained in how to obtain consent and understood that patients could refuse.

### *Intervention and control arms*

During the control phase, admission screening was by CS only. During the intervention, patients were screened by both CS and POCS and both results were reported as soon as they were available. If the POCS returned an error/invalid result, the test was not repeated and interpreted as “not positive”.

For CS, pooled swabs from nose, throat and perineum were cultured in MRSA selective broth and MRSA Chromagar (Oxoid, Basingstoke, UK). Swabs from lesions at other sites were processed similarly. Meticillin susceptibility was determined by disc or automated testing (VITEK2; Biomérieux, Basingstoke, UK).

The intervention was POCS using the Xpert<sup>TM</sup> MRSA system (Cepheid, Sunnyvale, CA, USA). A four-module Xpert system was installed in each of the study wards and POCS was performed by ward healthcare workers (HCWs) after training and confirmation of competency. Nasal swabs only were used for POCS, since these are the specimens licensed by the Food & Drug Administration for the system. Two nasal samples were taken simultaneously with double headed swabs (Copan, Brescia, Italy); one was used for CS and the other for POCS. Patients' MRSA discharge status was assessed by CS on pooled nose, throat and perineum swabs.

Standard infection prevention and control (IPC) precautions were implemented for all patients, as well as pre-emptive isolation of patients judged at risk of MRSA carriage.<sup>12,15</sup> MRSA positive patients were entered into an MRSA care pathway if they were known to be previously positive or as soon as a positive result was obtained from either POCS or CS; the management included decontamination and isolation (in side room, cohort bays or barrier isolation on wards, depending on the facilities available), following national guidelines.<sup>1,15</sup>



### *Data Collection*

We collected patient demographics, date and time of admission and discharge and physical status on admission (using the American Society of Anesthesiology [ASA] scoring system).<sup>16</sup> We collected potential ward confounding factors for MRSA transmission, including staffing levels; staff hand hygiene policy compliance (observed monthly); patient-days per month that MRSA positive patients were cohort/barrier isolated; and the MRSA importation pressure, defined as the proportion of patients positive for MRSA on admission per month.

We regarded MRSA culture screening specimens taken within 48 hours of admission and 48 hours after discharge as valid screens for the study. Patients who stayed for less than 48 hours were included only if both admission and discharge culture screens were performed during their ward stay. Patients who were MRSA culture positive in any specimen taken up to five days before admission were classified as MRSA admission positive.

### *Outcome Measures*

The primary outcome was the MRSA acquisition rate (the proportion of patients MRSA negative on admission who subsequently became MRSA positive by the time of discharge). Secondary outcomes were (1) the MRSA transmission rate (the ratio of patients MRSA positive on admission to the number of MRSA acquisitions); (2) the MRSA acquisition rate per 1,000 patient days; (3) the TATs for the screening tests; and (4) the performance characteristics of POCS compared with CS.

### *Statistical Analysis*

To assess the effect of the intervention on the primary outcome, we conducted a multilevel Poisson segmented regression allowing for ward-level random variation for baseline levels and time trends (from study start to end). We assessed step changes and changes in trends of MRSA acquisition rates per 100 patients at risk, in a model with a log link function adjusted by potential confounders (treated as continuous variables). We included an offset term in the natural logarithm scale to account for the monthly exposure in each ward (i.e. the total number of patients at risk of acquiring MRSA [MRSA negative on admission] that were discharged monthly). The dependent variable was the monthly number of patients negative on admission who acquired MRSA during the ward stay. The significance of fixed effects was assessed through Wald tests. Measures of association for the fixed terms were summarized by adjusted Incidence Rate Ratios (IRR) per 100 patients at risk. The maximal random effect structure justified by the data was determined by comparing models accommodating increasingly complex random structures through log likelihood ratio tests. The analysis was conducted in R-3.1.1. statistical software using the package 'glmmADMB' to fit multilevel models by Laplace approximation.<sup>17-19</sup> For robustness, model coefficients were compared to those obtained using the Penalized Quasi-Likelihood estimation method (glmmPQL) in the 'MASS' package.<sup>20,21</sup>

### **Results**

There were 13715 admissions to the study wards, 6680 (48.7%) in the control arm and 7035 (51.3%) in the intervention arm; 760 (5.5%) were not screened by CS for MRSA on admission and were excluded, leaving a total of 12955 patients in the study, 6219 in the control and 6736 in the intervention arm (Figure 1). Of these 12955, 222 (1.7%) were CS positive for MRSA on admission (or were known to be positive within the five days before admission) (control 113, 1.8%; intervention 109, 1.6%). POCS was performed on 6414 intervention arm admissions (91.2% of total admissions).

With CS as the reference standard, the sensitivity of POCS was 68.8%, specificity 97.2%, Positive Predictive Value 28.8% and Negative Predictive Value 99.5%. Error/invalid results occurred in 6.2% of tests and were excluded from this analysis. The median TAT from admission to reporting was 40.4 hours for CS and 3.7 hours for POCS ( $P<0.001$ ).

Of the 12733 patients who were MRSA culture negative on admission, 2716 (21.3%) were not correctly swabbed at discharge, due to either an oversight by staff or patients leaving the ward before the swabs were taken (control 1128, 18.5%; intervention 1588, 24.0%). Thus, there were 10017 patients who were CS negative on admission and had CS on discharge and were eligible for analysis (78.7% of all admissions screened by CS), 4978 control (81.5%) and 5039 intervention (76.0%) (Figure 1). The baseline patient and ward characteristics of patients in the two study wards were similar (Table II).

MRSA was acquired by 47 (0.47%) of all 10017 patients eligible for analysis, 23/4978 (0.46%) patients in the control arm and 24/5039 (0.48%) in the intervention arm (Table III).

The total number of days that MRSA admission positive patients were not isolated was 257 (67% of their total stay of 378.3 days) in the control arm and 205 (40.6% of their total stay of 504.8 days) in the intervention arm ( $P<0.001$ ).

There was no significant difference between patients in the control and intervention arms for age, gender, ASA score, study ward stay, days at risk for MRSA acquisition, being MRSA culture positive on admission but pre-emptively isolated before the positive result or length of ward stay of patients who were MRSA culture positive on admission. The segmented Poisson regression results showed that none of the confounding ward variables was a significant predictor of MRSA acquisition rate and no step change or trend change in MRSA acquisition rate was observed following the intervention. The results were consistent with those obtained when using the Penalized Quasi-Likelihood estimation method (data not shown).

Seven patients who were MRSA culture negative on admission and positive on discharge were POCS admission positive. When these cases were excluded from the analysis, there was still no difference in the acquisition rates between the two arms.

## Discussion

As in many other hospitals, we now have four acute admission wards for the initial admission and assessment of emergency patients, where they stay for around 1–3.5 days (mean 2 days) before being discharged home or transferred to general wards. Admission MRSA screening of emergency patients is therefore ideally done on admission to the admission wards. Because conventional CS takes 2-3 days, some CS results became available only after patients have left the admission ward. Rapid POCS can produce results within about one hour and is faster even than laboratory-based PCR testing, which produces results in about 22 hours. POCS on admission wards therefore should theoretically facilitate the efficient management of MRSA carriers, allowing them to be placed on the MRSA pathway hours or days earlier than with other screening methods. This would be expected to reduce MRSA transmission and acquisition both on the admission wards themselves and then on the general wards. If POCS does not have an impact on transmission and acquisition while on the admission ward, it would have no advantage over CS wherever it is used.

In order to test this hypothesis we performed a controlled clinical trial to measure the impact of POCS compared with CS on MRSA acquisition within the admission wards. We did this firstly because it is impossible to control for the numerous other factors that affect MRSA acquisition on general wards and secondly, if POCS does have a beneficial effect, it should be detectable within the first 24 - 48 hours. If it does not, then slower and cheaper screening methods would be appropriate. Furthermore, the risk of MRSA acquisition on the admission wards is significant; in the present study

there were about 20,000 patient hours of exposure to potential MRSA acquisition in each of the study arms.

We used a cluster-randomised cross-over study to compare CS and POCS (the intervention) screening on the four admission wards. The POCS test was implemented satisfactorily by HCWs, with performance characteristics similar to those reported by others.<sup>22-25</sup> When compared with CS, the Xpert MRSA specificity and NPV were good but the sensitivity and PPV were low. The low PPV result probably reflects a low prevalence of MRSA carriage at admission;<sup>26</sup> other possible contributory factors include poor sampling, detection of non-viable organisms, detection of meticillin resistance genes in other organisms such as coagulase-negative staphylococci or in gene fragments, or non-specific amplification.<sup>11</sup> The extra numbers of MRSA positive patients reported by POCS, compared with CS would have tended to increase rather than decrease early MRSA control for patients screened by POCS. However, the low sensitivity of POCS compared with CS reduced the proportion of CS positive patients that were detected more rapidly by POCS.

POCS produced significantly faster results than laboratory-based CS by some 37 hours, facilitating the much earlier implementation of appropriate MRSA control. As a result, in the control arm MRSA positive patients were isolated for 33% of their total stay while in the intervention arm positive patients were isolated for 59% of their total stay. The reason the positive patients in the intervention arm were not isolated for closer to 100% of their stay was that the POCS test had poor sensitivity (68.8%) when CS was used as the standard. This meant that around 30% of the CS-positive patients were not detected by POCS and were therefore not isolated until the CS result was returned.

Despite there being no significant difference between the control and intervention arms for patient age, gender, ASA score, length of ward stay, patient days at risk of MRSA acquisition or pre-emptive isolation, and allowing for variations in background MRSA importation pressure, staffing levels and compliance with hand hygiene, there

was no significant change in the MRSA acquisition rate following the intervention. Thus, we found no evidence to support the hypothesis that rapid POCS of patients on admission wards reduces rates of MRSA acquisition, and hence transmission on those wards compared with conventional, laboratory-based CS. POCS reduced the time that MRSA positive patients were not isolated compared with CS, but this did not reduce MRSA acquisition.

A cluster-randomised cross-over study was an appropriate design for this trial but it may have been under-powered. The MRSA importation pressure and the transmission and acquisition rates in the control arm were lower than expected and, although MRSA screening on the admission units best reflects present hospital practice, it limited the number of clusters for analysis. Although there were four clusters per arm, which is the required minimum, a larger number would have been desirable; with each ward as its own control it is not possible to ensure with four clusters that the two arms remained balanced over time.

Our study has some limitations. Only about three quarters of eligible patients had full admission and discharge screen data and, although there were about 5000 patients with full data sets in each arm, it is possible that we were unable to detect a small effect because rates of both MRSA carriage and transmission were low. The average length of stay on the admission wards was approximately 2 days and it can be argued that we may not have detected MRSA transmission by culture during this period; on the other hand, this is the time during which POCS would be expected to have a greater impact than CS. POCS significantly reduced the number of days that MRSA positive patients were not isolated compared with CS but this effect was reduced by the fact that the sensitivity and PPV of POCS on nasal swabs compared with CS on pooled multiple site swabs was low. These low values were partly the result of the low prevalence of MRSA carriage, but may also have been because (in culture studies) nasal swabs detect only around 80% of carriers compared with swabbing at multiple sites.<sup>9</sup> This is an inherent problem with this POCS test because it is licenced by the FDA for nasal swabs only.

In the present study the MRSA carriage rate at admission measured by CS was 1.71%. This is much lower than the rate of 6.7% found by CS in London hospitals in 2006-7,<sup>5,8</sup> but similar to the 1% result of a one week national prevalence study of MRSA screening in English NHS hospitals in 2011.<sup>27</sup> This decline in MRSA admission carriage reflects the overall fall in MRSA infection rates in English hospitals associated with a national programme of targeted improvements in MRSA prevention and control.<sup>13</sup> The lack of effect of rapid POCS in the present study may have been due to the low MRSA carriage rate at admission combined with good standard IPC practice, including pre-emptive isolation of higher risk patients.

It is likely that in a setting of low MRSA admission prevalence, good IPC can prevent most MRSA transmissions, even without admission screening, whether by standard or rapid methods.<sup>7,10,12</sup> Furthermore, Robotham *et al* have shown in mathematical modelling studies that universal admission and weekly screening using a PCR MRSA test coupled with isolation is unlikely to be cost effective unless the prevalence is high.<sup>28</sup>

Although the effectiveness of universal MRSA screening of all admissions has long been debated,<sup>4-7</sup> the Department of Health (England) previously recommended that hospitals should screen all admissions.<sup>29</sup> However, in 2014, the Department revised its guidance and recommended targeted screening of only high risk patients.<sup>13</sup> This view is supported by the present study, which has shown that there is presently a very low prevalence of MRSA carriage at admission in London.

In conclusion, there is growing evidence that in an environment where compliance with appropriate MRSA IPC procedures is high and the prevalence of MRSA carriage is low, rapid MRSA admission screening has no additional impact on MRSA acquisition and transmission compared with standard CS. The results of the present trial suggest that this is not only true for laboratory-based PCR tests but also for very rapid POC PCR screening. Our study does not support the introduction of point of care MRSA admission screening as a routine.

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## Conflict of Interests Statement

None declare

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**Table I Characteristics of study wards**

| <b>Ward Speciality</b>                                | <b>No. of beds in bays</b> | <b>Side rooms</b> | <b>Total beds</b> |
|---|----------------------------|-------------------|-------------------|
| Acute Surgical Unit (ASU, 6 bays)                     | 28                         | 3                 | 31                |
| Medical Admissions Unit 1 (MAU 1, 6 bays)             | 24                         | 6                 | 30                |
| Medical Admissions Unit 2 (MAU 2, 6 bays)             | 24                         | 6                 | 30                |
| Neurosurgical ward with High Dependency Unit (4 bays) | 21                         | 10                | 31                |

**Table II**

Baseline characteristics of all patients in the control and intervention wards (all differences between the control and intervention wards were non-significant)

| <b>Characteristics</b>  | <b>Control wards</b>  | <b>Intervention wards</b> |
|---|-----------------------|---------------------------|
| Median (interquartile range) age in years   | 57.2<br>(40.3 - 75.4) | 58.7<br>(41.0 - 76.5)     |
| Women (%)   | 3155<br>(47.2)        | 3367<br>(47.9)            |
| Median (interquartile range) ASA score*   | 2<br>(2 - 3)          | 2<br>(2 - 3)              |
| Median (interquartile range) study ward stay in days  | 1.9<br>(1.0 - 3.6)    | 2.0<br>(1.0- 3.7)         |
| Number of patients screened on admission or known to be MRSA positive                                     | 6219                  | 6736                      |
| Number patients MRSA positive at admission (% of screened admissions)                                     | 113 (1.8%)            | 109 (1.6%)                |
| MRSA culture positive on admission but pre-emptively isolated before positive result (% of all positives) | 33<br>(29.2)          | 48<br>(44.0)              |
| Median (interquartile range) study ward stay for patients who are MRSA culture positive on admission      | 2.0<br>(0.9 - 4.9)    | 3.0<br>(1.3 - 4.9)        |

|   |       |       |
|---|-------|-------|
| Number of patient-days that MRSA-negative patients were at risk of MRSA acquisition | 20956 | 23704 |
|---|-------|-------|

\*American Society of Anesthesiology score for physical status: from 1 (completely healthy) to 5 (moribund, not expected to live 24 hours)<sup>16</sup>.

**Table III**

Results for methicillin-resistant *Staphylococcus aureus* (MRSA) acquisition and transmission rates

| Variables  | Control arm    | Intervention arm | Total        |
|--|----------------|------------------|--------------|
| Number of patients who were screened by CS on admission (or were known to be positive) and discharge (%) | 4978<br>(74.5) | 5039<br>(71.6)   | 10017        |
| Number of patients MRSA positive by CS on admission (or were known to be positive) (%)                   | 113<br>(1.8)   | 109<br>(1.6)     | 222<br>(1.7) |
| Number of patients who acquired MRSA by discharge (MRSA acquisition rate, %)                             | 23<br>(0.46)   | 24<br>(0.48)     | 47<br>(0.47) |
| Acquisition per 1,000 patient-days   | 5.39           | 4.60             | 4.97         |
| Transmission rate  | 0.20           | 0.22             | 0.21         |

**Figure 1. Flow chart of the cross-over trial**

ACCEPTED MANUSCRIPT

